

### REMARKS

Paragraphs [0025]-[0089] are amended to remove references to paragraph numbers and to correct typographical errors. In particular,  $M^3$  in paragraph [0025] has been changed to  $M^4$ . The use of  $M^3$  rather than  $M^4$  is a typographical error which is obvious from the definitions of  $M^1$ ,  $M^2$ ,  $M^3$ , and  $M^4$  in paragraph [0024], to which paragraph [0025] refers. As described in [0024],  $M^3$  can only be  $-NR^9$ -,  $-O$ -, or absent;  $M^1$  cannot be a divalent group;  $M^2$  is always a ring; and  $M^4$  is  $-\text{CH}_2$ -,  $-\text{CH}_2\text{CH}_2$ -,  $-\text{CH}_2\text{CHCH}_2$ -, or absent. Thus,  $M^4$  is the only group that can be  $-\text{CH}_2$ -. In paragraph [0031], "piperizin" is misspelled and has been amended to "piperazin". In paragraph [0041], "q = one to three" has been amended to "q is one, two, or three". In paragraphs [0048], [0053]-[0056], and [0068], "the compounds of are" is amended to "the compound is". In paragraphs [0069] and [0076], "q = 3" is amended to "q is three". In paragraphs [0082]-[0089], "or the pharmaceutical composition" has been amended to "and optionally together with a pharmaceutically acceptable carrier," support for which is found in paragraph [0081]. Subject to the comments below, all of the remaining amendments to paragraphs [0026]-[0089] result from deletion of cross-references to prior paragraphs.

Paragraphs [0052]-[0058] have been amended so they no longer depend from the paragraphs which precede them because they are broader in scope than the paragraphs from which they depend. All the limitations have been incorporated. In addition, for clarification purposes, the following groups:

optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclalkylidyne, optionally substituted lower alkylidene, optionally substituted lower arylalkylidene, and optionally substituted lower heterocyclalkylidene

as listed in  $R^{13}$  in paragraph [0052] are amended to describe the valence state of each group.  $R^{13}$  is a monovalent group comprised of monovalent moieties that may be optionally substituted. Each group in the definition of  $R^{13}$  has been amended to recite the corresponding monovalent moiety. For example, "optionally substituted lower alkylidyne" has been changed to optionally substituted lower alkynyl. ("Alkylidyne"

indicates a bivalent moiety whereas “alkynyl” refers to the corresponding monovalent group).

Entries 1-4, 6-8, 16-17 in Table 1 have been amended to include structures depicting the 5r geometric isomer as recited in the corresponding names. In addition, the names of the original structures have been added to each entry. Similarly, entries 9-15 in Table 1 have been amended to include structures depicting the 5s geometric isomers as recited in the corresponding names. In addition, the names of the original structures have been added to each entry.

In Table 1, the chemical structures of entries 22-24 and 26-28 have been amended to depict the (3S,9aS) stereochemistry as recited in the corresponding names. The (3S,9aS) isomers and the related (3R,9aS) isomers are separately listed in Table 1. The structures for the (3R,9aS) isomers are accurately depicted (see Table 1, entries 29, 30, 21, 19, 18, and 20) where the (3S,9aS) isomers were not. By way of example, unamended entry 22 is as follows:

22	N-(3,4-dichloro-2-fluorophenyl)-7-[[ <b>(3S,9aS)</b> ]-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine (emphasis added)	
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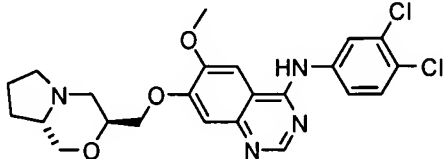
and its corresponding isomer is depicted in entry 29 as follows:

29	N-(3,4-dichloro-2-fluorophenyl)-7-[[ <b>(3R,9aS)</b> ]-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine (emphasis added)	
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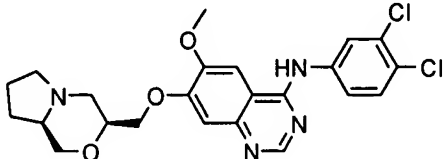
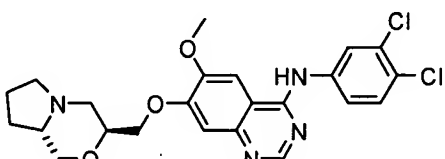
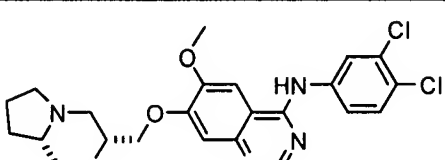
The structures for entries 22 and 29 are identical but the names are not – one is (3S,9aS) and the other is (3R,9aS). It is obvious that the (3R,9aS) structure of entry 29 was mistakenly duplicated for the (3S,9aS) isomer of entry 22. For the same reason, the errors in entries 23, 24, 26, 27, and 28 in Table 1 are obvious as well.

Similarly, the chemical structure of entry 31 in Table 1 has been amended to depict the (3R,8aR) stereochemistry as recited in the corresponding name. The related

(3S,8aR), (3S,8aS), and (3R,8aS) isomers are all listed in Table 1 (entries 33, 34, and 35, respectively) and their structures match their corresponding names. Unamended entry 31 is as follows

31	N-(3,4-dichlorophenyl)-7-[[ <b>(3R,8aR)</b> -hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy]-6-(methyloxy)quinazolin-4-amine (emphasis added)	
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and entries 33, 34, and 35 are as follows

33	N-(3,4-dichlorophenyl)-7-[[ <b>(3S,8aR)</b> -hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy]-6-(methyloxy)quinazolin-4-amine (emphasis added)	
34	N-(3,4-dichlorophenyl)-7-[[ <b>(3S,8aS)</b> -hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy]-6-(methyloxy)quinazolin-4-amine (emphasis added)	
35	N-(3,4-dichlorophenyl)-7-[[ <b>(3R,8aS)</b> -hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy]-6-(methyloxy)quinazolin-4-amine (emphasis added)	

The structure of entry 31 is the same as that for 34. It is obvious that the structure of entry 31 was misdrawn.

Paragraph [0113] is amended to remove “potentially ad infinitum.”

Paragraph [0189] is amended to include parentheses around “difluoromethyl.”

Paragraph [0194] is deleted because of a naming error in the compound name.

The D-glucitol isomer was actually prepared and not the L-glucitol isomer although the D-glucitol isomer could be prepared using analogous techniques.

Example 4, encompassing paragraphs [0202]-[0207] and the three lines preceding paragraph [0202], are amended to correct mistakes in naming. In the first line of paragraph [0202], a typographical error was made in the name of the starting material.

“Glycitol” has no meaning in the context of this example and should be glucitol. In addition to this typographical error, the product of the reaction described in paragraph [0202] is misnamed. A person of ordinary skill in the art would recognize that the reaction necessarily produces “1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-*D*-arabino-hex-1-enitol” and not “1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-*L*-arabino-hex-1-enitol” when reacting the starting material 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-(*D*)-glucitol as described. This naming mistake was propagated in the subsequent steps. Methyl 3,6-anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl- $\alpha$ -*L*-idofuranoside was the compound that was actually prepared and is the only product possible when starting with 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-(*D*)-glucitol.

Example 5, encompassing paragraphs [0208]-[0211] and the three lines preceding paragraph [0208], has been deleted because of a naming error in the starting material in the first step of this example.

Paragraph [0248] is amended to include “[4-” and a missing parenthesis. Following the steps described in Example 12, the product in paragraph [0248] is necessarily (3*S*,8*aS*)-3-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one.

Paragraph [0260] is amended to add a missing bracket to the name “*N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3*aR*,5*r*,6*aS*)-octahydrocyclopenta[*c*]pyrrol-5-yl]methyl]oxy}quinazolin-4-amine hydro-chloride” and to correct the molecular formula given for this compound. The molecular formula for the product of the reaction described in paragraph [0259] was inadvertently copied for the product of the reaction described in paragraph [0260]. One of ordinary skill in the art would recognize that the molecular formula is correct for paragraph [0259] and incorrect for paragraph [0260] and that the product as named in paragraph [0260] is necessarily the compound obtained.

Paragraph [0274] and the compound name in the title of Example 17 have been amended to include the 5*r* designation which was inadvertently dropped in the product of this example. A person of ordinary skill in the art would recognize that the reaction conditions used to derivatize the starting material: *N*-(4-bromo-3-chloro-2-fluorophenyl)-

6-(methoxy)-7-{{[(3*R*,5*r*,6*S*)-octahydrocyclopenta[*c*]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine hydrobromide, and the subsequent workup of the product, would necessarily yield the 5*r* geometric isomer and would recognize that the NMR data demonstrates that a single isomer was present.

Example 18, encompassing paragraphs [0278]-[0282] and the three lines preceding paragraph [0278], is amended to correct mistakes in the naming of the title compound and in the naming of intermediates in the synthesis of the title compound. A bracket is missing in the name of the title compound, but is found in the name of the product at the end of the last step. In addition, the final product of this example is inaccurately named as the 5*r* isomer. The 5*r*/5*s* composition of the final compound was, in fact, not determined. A person of ordinary skill in the art would recognize that the compound *N*-(3,4-dichlorophenyl)-7-({[(3*R*,6*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]}oxy)-6-(methoxy)quinazolin-4-amine would be produced by this reaction.

Paragraphs [0317]-[0371] on pages 139-147 of the Specification are deleted because of naming errors in the compounds of paragraphs [0318]-[0371]. The L-itol isomers were actually prepared and not the D-itol isomers although the D-itol isomers could be prepared using the techniques described.

Paragraph [0411] is amended to add a dash missing from the name.

Entries 2, 3, 4, 5, 6, 7, 31, 33, 34, 35, 37, 45, 47, 48, and 50 in Table 3 and entry 252 in Table 6 have been deleted because of mistakes in the compound names. Entries 2, 3, 4, 5, 6, and 7 are designated as the 5*s* isomer. The 5*r* isomers were the ones actually tested. For entries 31, 33, 34, and 35, the D-glucitol isomers were the ones actually tested and not the D-xylo-hexitol isomers as named in the table. For entry 37, the D-mannitol isomer was tested and not the D-threo-hexitol as named in the table. For entries 45, 47, 48, and 50 the endo, endo, endo, and exo designations, respectively, were the ones tested and not the mixture of geometric isomers as the names indicate. For entry 252 in Table 6, the L-itol isomer was tested and not the D-glucitol isomer as named in the table. Entries 1-54 of Table 4 have been deleted because of mistakes in the compound

names. Each of these compounds was designated as D-iditol isomers, but the L-iditol isomers were the ones actually tested.

Support for the above corrections and for new Claims 67-134 are found throughout the Specification. The above corrections and new claims are done to particularly point out and distinctly claim what the Applicants regard as their invention.

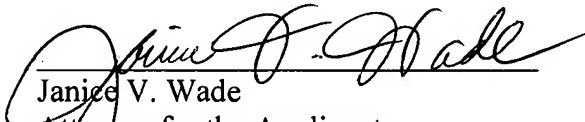
#### SUMMARY

The Applicants believe that no new matter is introduced with the above amendments and new claims. The Applicants respectfully request that the amendments and new claims be entered into the record.

It is believed that no fees are required with the submission of this preliminary amendment, however, should a fee be necessary, the Commissioner is hereby authorized to charge any necessary fee to Deposit Account Number 50-1108.

Respectfully submitted,

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Date

  
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